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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,794	DIME ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-63* is/are rejected.

7)☒ Claim(s) *46, 48-50, 53, 55-57, 62 and 64-66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 44-66 are pending.

Applicant's amendments filed on December 9, 2002 (Paper No. 19) is acknowledged, and applicants' response has been fully considered. Claims 44, 51-52, 57-59, 62 and 66 have been amended. Therefore, claims 44-66 are examined.

Objection Withdrawn

2. The previous objection to the disclosure regarding Figure 1D and Figure 1E, is withdrawn in view of applicants' amendment to the specification in Paper No. 19.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 44-66 under 35 USC § 112, second paragraph, regarding "a chemically reactive group" (claims 44-66), "the drug having anchoring moiety" in claim 46, "a dithiopyridyl group, a reactive disulfide" in claims 50, 57 and 66, "said compound" and "A is a drug" in claim 51, "said biological target molecule comprises a protein target and a bifunctionally chemically reactive group" in claim 58, "on a protein" or "A or D being identified as a drug" in claim 59, or antecedent basis in claim 65, or the claim containing non-elected inventions, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 6-10 in Paper No. 19.

Informalities

The disclosure is objected to because of the following informalities:

4. The numbering of Fig. 5A-Fig. 5H has been changed, and Fig. 8 has been amended, however, clean copies of the drawings have not been provided. Clean copies of Fig. 5A-5D and Fig. 8 are required.

Claim Objections

5. Claims 46, 48, 49, 50, 53, 55-57, 62, 64-66 are objected to because the claim contains non-elected inventions.

In response, applicants indicate the species election was made merely for search purposes under MPEP 803.02 , should no prior art be found that anticipated or renders obvious the elected species, the search of the Markush-type claims will be extended (paragraph 7 of the response). The argument is not found persuasive because the unity of invention exists when compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility under MPEP 803.02, however, in the instant case, e.g., the drug in claim 46 is a member of the group consisting of a peptide, a random bio-oligomer, a benzodiazepine, a hydantoin, a nonpeptidal peptidomimetic.....a nucleic acid, antibody.....and a local anesthetic, which do not have the same utility, nor share a substantial structural feature, these compounds are not considered as a Markush group having the unity of invention, thus the non-elected members are patentably distinct inventions from the elected compound and are withdrawn form consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 44-58 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-58 are indefinite because the claim indicates the drug that binds at a preselected target site on a biological molecule, it also indicates the drug is linked to an anchoring moiety which is specific for the chemically reactive group at the preselected target site and forms covalent bond, it is not clear whether the drug binds at the preselected target site via the anchoring group, or, the drug itself also binds to the same preselected target site and how the drug binds to the target site. Claims 45-51 and 53-58 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

7. Claim 45 is indefinite because the claim cites the drug having anchoring moiety, however, the independent claim 44 cites the drug is linked to anchoring moiety, thus, it is not clear whether the drug contains the anchoring group or not.

8. Claims 47, 54 and 63 are indefinite because of the use of the term "said biological target molecule is on a protein". The term "said biological target molecule is on a protein" renders the claim indefinite, it is unclear what molecule is as to the biological target molecule on a protein, and how the biological target molecule is related to the protein.

In response, applicants indicate the specification has shown the anchoring group can react with a selected number of functional groups that are present on the protein, and a person of ordinary skill in the art would recognize the nature and relation of the biological target molecule to the protein (paragraph 9 of the response). The argument is not found persuasive because the

claim does not indicate the biological target molecule is "an element" of the protein such as the functional group of the amino acid residue on the protein, and the claim reads the biological target molecule which can be a separate molecule on the protein.

Claim Rejections - 35 USC § 102/103(a)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 44, 47 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Greenfield *et al.* (EP 0398305).

Greenfield *et al.* teach a method for delivering the cytotoxic anthracyclines to eliminate a selected population of cells using a conjugate of anthracycline with a cell reactive molecule such as antibody or a ligand of EGF or bombesin (an anchoring group) via a linker (abstract; page 4, lines 49-51; page 7, lines 41-44; claims 44 and 51). The antigen and EGF receptors are proteins where the side chains of amino acid residues such as amino, carboxyl and thiol groups are chemically reactive groups, and the antibodies of the conjugate bind tumor-associated antigen (page 8, lines 19-23) and the ligand EGF of the conjugate bind the EGF receptors of the tumor

cell (page 8, lines 43-50; claim 47). Thus, the reference makes obvious if not anticipated to the claimed method for identifying a drug linked to an anchoring moiety, which binds a target site of a biological molecule.

In response, applicants indicate Greenfield *et al.* teach the anthracycline molecule of the drug conjugate does not interact with a specific receptor target, the conjugate has only a single specific binding moiety that is designed to deliver an anthracycline molecule to produce non-elective cytotoxicity, while the present invention is directed to both the anchor and the drug are specific to a molecular target, the drug portion will interact selectively with a receptor site on the same protein to which the drug is anchored, and claim 44 indicates the anchor and the drug interact with a selected site on specific target proteins (pages 11-12 of the response). The argument is not found persuasive because the claim only indicates the drug is linked to an anchoring moiety which is specific to a chemically reactive group at the preselected target site, thus, it appears the drug binds to the preselected target site via the anchoring moiety. The claim does not indicate the drug interacts selectively with a receptor site on the same protein to which the drug is anchored, nor shows how the drug binds to the selected site on specific target proteins.

10. Claims 44, 47, 49-52, 54 and 56-58 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Pouletty *et al.* (WO 95/10302).

Pouletty *et al.* teach bifunctional reagents or conjugates of an anchor and a physiologically active entity (the first binding entity or target binding member), where the reagent is bound through an anchor to a long lived moiety associated with the blood, either

cellular or a mobile blood protein (page 2, lines 8-14; claims 44, 47). The anchor and the target binding moiety can be connected by covalent bond in a single member conjugate (page 13, lines 29-35), and the two can also be covalently linked by an appropriate chain (page 27, lines 12-15; claim 51). Binding of the reagent to the long-lived blood protein may be specific or covalent (page 11, lines 29-35; clam 52, 54), and the functional groups on the protein are amino, carboxyl, and thiol groups which can be used as the target for reactive functionality of the reagent to form amide, ester and disulfide, and a number of bifunctional compounds for linking to entities are provided (page 17, line 32-page 19, line 1; Examples; claims 49-50 and 56-58). The first binding entity may be a ligand for a naturally occurring receptor, a substrate for an enzyme (page 20, lines 14-17). Thus, the reference makes obvious if not anticipated to the claimed method for identifying a drug linked to an anchoring moiety, which binds a target site of a biological molecule.

In response, applicants indicate Pouletty *et al.* disclose the drug conjugates that bind to a long-lived blood component entity, it does not teach the binding of the anchor facilitates the binding of the drug to the same target tissue or protein, while the present invention is directed to the anchor binds to the target protein, the binding of the drug is facilitated by the binding of the anchor as a direct result of the juxtaposition of the binding site for the anchor and the binding site for the drug, where the binding sites of the anchor and the drug on the same protein are in close proximity to one another (pages 12-13 of the response). The argument is not found persuasive because the claim only indicates the drug is linked to an anchoring moiety which is specific to a chemically reactive group at the preselected target site and forms covalent bond, thus, it appears the drug binds to the preselected target site via the anchoring moiety. The claim does not

indicate the drug interacts selectively with a receptor site on the same protein to which the drug is anchored, nor shows how the drug binds to the selected site on specific target proteins.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 59-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Fesik *et al.* (U. S. Patent 5,989,827, filed October 1996).

Fesik *et al.* teach a method for identifying compounds as new drug leads, which bind to a given target biomolecule (e.g., protein). The method comprises identifying a first ligand to the target molecule using two-dimensional $^{15}N/^{1}H$ NMR correlation spectroscopy; identifying a second ligand to the target molecule using two-dimensional $^{15}N/^{1}H$ NMR correlation spectroscopy; forming a ternary complex by binding the first and second ligand to the target molecule; determining the spatial orientation of the first and the second ligand on the target molecule; and linking the first and second ligand to form a drug using an appropriate linking

group to maintain the spatial orientation (column 2, lines 33-62; Examples 1-5; claim 59). The first and second ligands can be selected from a collection of compounds on the basis of size and molecular diversity (column 8, lines 25-36; claims 60 and 61).

In response, applicants indicate Fesik *et al.* teach a process for the design and identification of compounds that bind to a chosen target biomolecule comprising 5 steps, and the two ligands are identified separately from one another, and then linked only in the step 5 of the process, while the instant invention is directed to a process of identifying the binding moieties while they are linked together by a linking group, therefore, the linking of the two binding moieties took place prior to the identification steps (pages 13-14 of the response). The argument is not found persuasive because the claim indicates a process of identifying the binding moieties such as the anchoring moiety and the drug, where they are linked together by a linking group, as the claim written, the claimed method does not differentiate from the teaching by Fesik *et al.* which is identifying compounds containing two ligands that bind to a chosen target biomolecule, where the two ligands are linked by an appropriate linking group,

Conclusion

12. Claims 44-63 are rejected, and claims 46, 48-50, 53, 55-57, 62 and 64-66 are objected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

Christopher S. F. Low

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February 28, 2003

CHRISTOPHER S. F. LOW
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